Attorney Docket No.: RTS-0175
Inventors: Monia and Ward
Serial No.: 09/865,993
Filing Date: May 25, 2001
Page 2

15. (amended) A method of inhibiting the expression of dual specific phosphatase 5 in cells or tissues comprising contacting said cells or tissues *in vitro* with the antisense compound of claim 1 so that expression of dual specific phosphatase 5 is inhibited.

## REMARKS

Claims 1, 2 and 4-20 are pending in the instant application. Claims 1, 2 and 4-20 have been rejected. Claims 11 and 16-20 have been canceled. Claim 15 has been amended. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

### I. Rejection of Claims Under 35 U.S.C. 112, Second Paragraph

Claim 11 has been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention. The Examiner suggests that the term "active site" is vague and unclear. Claim 11 has been canceled making this moot. Withdrawal of this rejection is respectfully requested.

**II. Rejection of Claims Under 35 U.S.C. 112, First Paragraph**

Claims 15-20 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject-matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner acknowledges that the specification while being enabling for *in vitro* antisense inhibition of dual specific phosphatase 5 expression does not reasonably provide enablement for *in vivo* antisense inhibition of dual specific phosphatase 5 expression; the Examiner cites several articles on the technology of antisense to support this position. Applicants respectfully traverse this rejection of the claims.

Applicants disagree with the Examiner's suggestion that cited references support the position that application of antisense *in vivo* is highly unpredictable.

The Examiner has pointed to six articles and a press release on the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable. However, when one reads each of the papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness

of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed in cells in the instant invention would also occur in cells in animals and humans.

The paper by Crooke is a review paper on the basic principles of antisense therapeutics. The statements alluded to by the Examiner concerning extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are only one small part of this review paper. When read in its entirety the author is merely stating a well known fact in the development of any drug, not merely antisense. Pharmacokinetics is not the study of the pharmacological activity of an agent, such as is studied commonly in cells, but rather the study of the biological distribution of a drug in an animal or human. Therefore, the statements by the author do not demonstrate the unpredictability of antisense oligos *in vivo* but rather merely state the obvious, that one would not use studies on cellular uptake to predict pharmacokinetics in animals or humans because it is not a logical use of such data for any drug. Data in cells are used routinely, however, as predictors of pharmacological activity in animals and humans. It is a fundamental principle of drug development that data from whole cell studies, such as are provided in the instant

specification, are directly applicable to predicting *in vivo* activity. The teachings of the paper by Crooke and the other cited review paper (Branch) provide no reason to doubt that this fundamental principle is applicable to antisense agents.

In fact, statements in the paper by Crooke support the fact that development of antisense drug products is viewed by those of skill in the art as being the same as development of any other drug product in terms of applying the basic principles of pharmacology. For example, on page 22, first paragraph, Crooke points out "...numerous well-controlled [pharmacological] studies have been reported in which antisense activity was conclusively demonstrated [*in vitro*]." The key according to Crooke is the careful design of the *in vitro* studies to carefully evaluate dose-response relationships and antisense mechanism, similar to the type of studies presented in the instant specification. Therefore, what this paper, and the other cited by the Examiner actually teach is that antisense oligonucleotides must be developed using well designed studies that progress logically from activity in cells to activity in animals and humans. Nowhere in the reference does the author state or suggest that results of well-designed *in vitro*

pharmacological studies would not be predictive of activity *in vivo*.

Moreover, the paper by Branch (1998) teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

The paper by Palu et al. (1999) is a review paper on the technology of gene therapy, not antisense. Gene therapy is an entirely different technology with its own set of issues for drug development. Citing this paper to support the unpredictability of antisense is inappropriate. Nowhere does this paper state that extrapolation from *in vitro* data on antisense compounds to *in vivo* effects is unpredictable.

The paper by Agrawal and Kandimalla (2000) is another review paper on the technology of antisense. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

The paper by Chirila et al. (2002) is a review of the use of polymers for delivery of antisense compounds. Although this paper reviews problems that have arisen during development of antisense,

problems that are addressed and solved in the specification as filed, nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

Finally, the press release cited by the Examiner does not support the conclusion that data from *in vitro* studies is not predictive of *in vivo* activity. This failure of a clinical trial for Crohn's disease is a very different standard where a drug must be statistically significantly better than a placebo on a particular endpoint. It does not mean the drug was without activity to inhibit gene expression when results from *in vitro* studies are extrapolated to *in vivo* activity.

However, in an earnest effort to advance the prosecution of this case, Applicants have amended claim 15 and canceled claims 16-20, with Applicants reserving the right to file a continuing application directed to this subject matter without prejudice. Withdrawal of the rejection is requested in light of these amendments.

**III. Rejection of Claims Under 35 U.S.C. 103(a)**

Claims 1, 2 and 4-14 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Ishibashi et al. (1994), in view of

Milner et al. (1997) and Baracchini et al. (US Patent 5,801,154). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill to design and use antisense molecules for inhibition of dual specific phosphatase 5 expression since the sequence encoding the gene was known (Ishibashi et al. 1994), that methods of designing and screening for antisense have been taught by Milner et al., and Baracchini et al. teach modification of antisense as claimed. The Examiner suggests one of skill would have been motivated to do so by the teachings of Ishibashi et al. in teaching the involvement of this gene in cellular processes. The Examiner suggests an expectation of success is provided by the teaching of Baracchini et al. in teaching the advantages of modified oligonucleotides for activity and stability. Applicants respectfully disagree with the Examiner's conclusions.

Ishibashi et al. (1994) discloses the sequence of human dual specific phosphatase 5. As acknowledged by the Examiner, nowhere does this reference teach or suggest antisense compounds of any type targeted to dual specific phosphatase 5 nucleic acid molecules as claimed. Therefore, this primary reference fails to teach the limitations of the claims as amended.

The secondary references cited, even when combined with this primary reference, fail to overcome the deficiencies in teaching of the primary reference.

Milner et al. teach a method for identifying antisense oligonucleotides using optimization techniques where the antisense oligonucleotides have 1-17 bases and target sequences of a gene. However, nowhere does this paper teach or suggest antisense oligonucleotides 8 to 50 nucleobases in length targeted to dual specific phosphatase 5.

Baracchini et al. (US Patent 5,801,154) teaches methods of modifying antisense oligonucleotides to enhance activity. However, nowhere do this patent teach or suggest antisense oligonucleotides 8 to 50 nucleobases in length targeted to dual specific phosphatase 5 nucleic acid molecules.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly, the combination of prior art cited fails to teach or

suggest the limitations of the claims, which claim antisense compounds targeted to a nucleic acid molecule (SEQ ID NO: 10) encoding dual specific phosphatase 5, and thus cannot render the instant claimed invention obvious. It is only with the specification in hand that one of skill would see that antisense compounds could be used successfully to inhibit expression of this gene. Further, there is no suggestion provided in the references themselves to combine reference teachings, as required under 35 U.S.C. 103(a). Accordingly, withdrawal of this rejection is respectfully requested.

## IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attorney Docket No.: RTS-0175
Inventors: Monia and Ward
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Page 11

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Respectfully submitted,

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Date: **February 19, 2003**

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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

In the Claims:

Claims 11 and 16-20 have been canceled without prejudice.

Claim 15 has been amended as follows:

15. (amended) A method of inhibiting the expression of dual specific phosphatase 5 in cells or tissues comprising contacting said cells or tissues *in vitro* with the antisense compound of claim 1 so that expression of dual specific phosphatase 5 is inhibited.